Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Toxicon 93 (2015) 125–135

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Review

Scorpion venom components as potential candidates for drug development

Ernesto Ortiz [a], Georgina B. Gurrola [a], Elisabeth Ferroni Schwartz [b], Lourival D. Possani [a, *]

[a] Departamento de Medicina Molecular y Bioprocesos, Instituto de Biotecnología, Universidad Nacional Autonóma de México, Avenida Universidad 2001, Cuernavaca 62210, Mexico
[b] Departamento de Ciências Fisiológicas, Instituto de Ciências Biológicas, Universidade de Brasília, Brasília 70910-900, DF, Brazil

ARTICLE INFO

Article history:
Received 24 September 2014
Accepted 25 November 2014
Available online 26 November 2014

Keywords:
Anticancer peptides
Antimicrobials
Bradykinin-potentiating peptides
Drug candidates
Immune-modulators
Scorpion venom

ABSTRACT

Scorpions are well known for their dangerous stings that can result in severe consequences for human beings, including death. Neurotoxins present in their venoms are responsible for their toxicity. Due to their medical relevance, toxins have been the driving force in the scorpion natural compounds research field. On the other hand, for thousands of years, scorpions and their venoms have been applied in traditional medicine, mainly in Asia and Africa. With the remarkable growth in the number of characterized scorpion venom components, several drug candidates have been found with the potential to tackle many of the emerging global medical threats. Scorpions have become a valuable source of biologically active molecules, from novel antibiotics to potential anticancer therapeutics. Other venom components have drawn attention as useful scaffolds for the development of drugs. This review summarizes the most promising candidates for drug development that have been isolated from scorpion venoms.

1. Introduction

Scorpions constitute a very well adapted order of predatory animals that have been living in the Earth for nearly 400 million years (Polis, 1990). They now inhabit virtually every terrestrial habitat, except Antarctica. More than 1700 species have been described to date (Stockmann and Ythier, 2010). The key to their success is the production of potent venoms that they use primarily to kill or paralyze their preys and to deter possible competitors and predators. The expansion of human civilization and the growth of human population have led to increased interaction with these arthropods, frequently resulting in accidents when people get stung (Chippaux and Goyffon, 2008). The immediate pain that the sting elicits and the devastating consequences that the envenomation can ultimately cause in human beings can be credited for the bad reputation of these animals.

The effects of a scorpion sting can vary widely, from just local pain or inflammation to severe clinical complications, including death. The severity of scorpion envenomation is related to the presence of neurotoxins in the venom (see recent review: Quintero-Hernandez et al., 2013). They can block or modify the functioning of their targeted ion channels in excitable cells, which results in autonomic excitation. Scorpion α-toxins cause massive endogenous release of catecholamines. The combination of sympathetic excitation and the release of catecholamines in plasma generates a cascade of physiological events that can progress to arterial hypertension or hypotension, tachycardia or bradycardia, arrhythmia, unconsciousness, pulmonary edema, heart failure and death (Isbister and Bawaskar, 2014). Scorpionism represents a major health problem in several countries. More than 1.2 million scorpion stings are registered globally every year. Despite the fact that only about 30 scorpion species are known to be dangerous to humans, about 3000 stings per year are fatal (Chippaux, 2012).

Scorpions, on the other side, have been used in traditional medicine since the emergence of ancient cultures, mainly in Asia and Africa (Goudet et al., 2002; Shao et al., 2007). Scorpions, their body parts, or their venoms, are claimed to be effective for the treatment of many conditions, including cancer (Das Gupta et al., 2007; Diaz-Garcia et al., 2013; Goudet et al., 2002). With the advent of novel methodologies for the massive study and characterization of venom components, it has become evident that along with toxins, many other peptides are present in the scorpion venoms. Several of these peptides are biologically active and have

* Corresponding author.
E-mail address: possani@ibt.unam.mx (L.D. Possani).

http://dx.doi.org/10.1016/j.toxicon.2014.11.233
0041-0101/

proven to be valuable tools for the development of drugs for the treatment of many important diseases.

2. Scorpion venom components

Scorpion venoms are highly complex mixtures of peptides, enzymes, mucoproteins, free amino acids, nucleotides, lipids, amines, heterocyclic components, inorganic salts and probably other unknown substances. Toxins are the most thoroughly studied scorpion venom components. This is due to their pharmacological action on ion channels and their clinical relevance as neurotoxins. They are disulfide-bridged peptides with a significantly constrained structure. Toxins that act on sodium channels are the most relevant for their effects on mammals, including humans. They can be classified into two main types: α-toxins that delay the voltage-gated Na^+-channel's inactivation, and β-toxins that trigger the opening of the channels at more negative potentials (Rodriguez de la Vega and Possani, 2005). In low doses, α-toxins provoke a strong depolarization of the cell membrane, followed by a drop in excitability. At higher doses they prolong the action potential of excitable cells and induce paralysis and cardiac arrhythmia (Bosmans and Tytgat, 2007). The action of β-toxins results in myoclonic or spastic muscular responses (Chippaux, 2012). Other characterized scorpion toxins act on potassium, chlorine and calcium channels. Though they can display synergistic actions leading to clinical manifestations, their role in human envenomation seems to be subsidiary. Toxins or toxin-related scorpion venom components are best known for their deleterious effects on cells, tissues and organisms, but paradoxically, some of them have been shown to display activities that might be relevant for the development of pharmaceutical drugs. These include antimicrobial, antimalarial, immunosuppressing and anticancer activities.

Among the other components present in scorpion venoms are the non-disulfide-bridged peptides (NDBPs) (Zeng et al., 2005, 2002). The NDBP group represents a major component of the scorpion venoms. Mass-fingerprint studies involving whole venoms have consistently shown that low molecular weight peptides represent more than a third of all the molecular weights that are determined (Rodriguez de la Vega et al., 2010). Since the main research interest was usually shifted towards the higher molecular weight peptides in the toxic venom fractions, the discovery rate of NDBPs was lagging till the last decade, as compared to the available information on toxins. The finding that NDBPs can exhibit relevant biological activities has drawn significant attention from researchers. This, together with the availability of molecular biology techniques, as cDNA library construction, heterologous expression, and lately, RNA-Seq have resulted in the increase of the available information on these small peptides (Quintero-Hernandez et al., 2011). Still, while several hundred toxins have been isolated from the scorpion venoms and described, just a few dozen NDBPs have been characterized thus far (Almaaytah and Albalas, 2014).

The venom components belonging to de NDBP group are small 13 to 56 amino acids-long peptides, with very diverse sequences. Most of them are cationic and display a remarkable structural flexibility. They exist in random coil conformations in aqueous solutions, but readily adopt amphipathic α-helical structures when placed in membrane mimicking environments, such as 50–60% aqueous trifluoroethanol (TFE). Positively charged NDBPs can easily interact with the negatively charged lipid head groups of the biological membranes. The membrane adhesion process drives the formation of the amphipathic helix and the insertion of the hydrophobic residues into the membrane, which leads to their displayed activity (Huang et al., 2010). This mechanism, in which there is no specific molecular target, results in their broad spectrum of biological targets. Several NDBPs exhibit multifunctional activities regardless of the target cells. This stands in sharp contrast with the mechanism of toxin action, since toxins are targeted against specific receptors (ion channels) from specific biological targets.

Several relevant activities have been described for the characterized scorpion venom NDBPs, including antibacterial, antifungal, cytolytic, antiviral, antimalarial, anticancer, bradykinin potentiating and immuno-modulating activities (Almaaytah and Albalas, 2014). This discovery has put the NDBP as very interesting and promising candidates for therapeutic drugs.

Hereafter, we will describe the diverse activities reported for scorpion venom components that could be relevant for the design and development of new pharmacological drugs. The molecules that constitute the most significant and promising candidates will be particularly covered.

2.1. Antibacterial peptides

The emergence of bacteria that are resistant to available antibiotics represents a first-line problem for the world health systems. Several pathogens that were once sensible to antibiotics are now rapidly becoming multi-resistant. Diverse bacterial mechanisms are responsible for the appearance of multi-resistance, including their rapid generation rates and chromosomal mutations, the acquisition of extra-chromosomal mobile DNA elements from other bacteria in the surroundings, together with some intrinsic mechanisms conferring the capacity to expel antibiotics from the cells (Alekshun and Levy, 2007). Once a multi-resistant organism emerges, it spreads in the human population, severely compromising the treatment of infections and thus provoking public health crises. This has reduced the long-term therapeutic value of many classical antibiotics and has forced the search for new antimicrobial candidates able to cope with the bacterial mechanisms of drug resistance (Gould and Bal, 2013).

Antimicrobial peptides (AMPs) are found in a very diverse range of phyla, from bacteria to mammals, including humans (Maroti et al., 2011). More than 2000 have already been described (Wang et al., 2009). In multicellular organisms they constitute primitive and conserved components of the innate immune system, functioning as a first barrier against many pathogens. Thanks to their broad spectrum of activities and targets, rapid action, and the low potential to induce resistance, AMPs have become promising prospects for new antibiotics (Huang et al., 2010; Mookherjee and Hancock, 2007). They kill microbes mainly by membrane-targeting pore-forming mechanisms that are inherently more difficult for microbes to circumvent by developing resistance (Hancock and Sahl, 2006). A significant fraction of the functionally characterized scorpion venom NDBPs displays antimicrobial activities, so they can be considered as AMPs (Almaaytah and Albalas, 2014; Harrison et al., 2014). It is not clear why they are present in the scorpion venom. They could play a synergistic role in facilitating venom activity or be part of the antimicrobial response within the venom gland (Kuhn-Nentwig, 2003). The pair of venom glands present in the last postabdominal segment (telson) of the scorpions has open communication with the environment, which can facilitate contamination by saprophytic organisms of the soil. Thus, scorpions are expected to possess means of defending themselves from the microorganisms present in the environment.

The first AMPs found in scorpion venoms were hadrurin from *Hadrurus aztecus* (now renamed as *Hadrurus gertschi*) (Torres-Larios et al., 2000), scorpine (Conde et al., 2000) and pandinins (Corzo et al., 2001) from *Pandinus imperator*, IsCTs from *Opisthacanthus madagascariensis* (Dai et al., 2001), opistoporins from *Opistophtalmus carinatus* and parabutoporin from *Parabuthus schlechteri* (Moerman et al., 2002). The main drawback of AMPs in general, is their frequent cytotoxicity against eukaryotic cells,

which limits their clinical applications. This is a problem shared by scorpion AMPs. For many scorpion NDBPs the potential therapeutic concentration (the Minimum Inhibitory Concentration, MIC) against the tested microorganisms is very close to the concentration at which they are cytotoxic to mammalian cells (usually measured in erythrocyte hemolysis assays). For example, hadrurin, the first scorpion NDBP shown to display antibacterial activity, was able to inhibit the growth of both Gram-positive and Gram-negative bacteria with a MIC of 10–50 μM, but was also highly hemolytic to human erythrocytes at 30 μM (Torres-Larios et al., 2000). This antimicrobial-hemolytic duality repeated itself for almost all scorpion AMPs described to date. It is for this reason that they were first proposed as prospective antimicrobials for topical applications only (Zeng et al., 2005). Nevertheless, some NDBPs showed a relatively mild cytotoxic effect, which improves their therapeutic index (the ratio given by the toxic dose divided by the therapeutic dose). The first example was Pandinin1, which effectively inhibited the growth of Gram-positive bacteria with a MIC of 2–6 μM, while keeping hemolysis very low at concentrations of up to 21 μM (1.4%, essayed on sheep erythrocytes) (Corzo et al., 2001). BmKbpp is a multifunctional peptide from the scorpion *Mesobuthus martensii* Karsch, with antimicrobial, immune-regulatory and bradykinin-potentiating activities (see below). BmKbpp demonstrated strong antimicrobial activity against Gram-negative bacteria with a MIC range of 2.3–4.7 μM. It was also active against a few Gram-positive bacteria, but with higher MIC. Its hemolytic activity can be considered to be mild, with 40% hemolysis of human erythrocytes at the relatively high 50 μM concentration (Zeng et al., 2012). VmCT1, an antimicrobial peptide synthesized from the precursor DNA sequence found in a cDNA library from *Vaejovis mexicanus smithi*, was effective against Gram-positive and Gram-negative bacteria with a MIC of 5–25 μM, and showed only mild hemolysis (12% against human erythrocytes) at an even higher concentration of 50 μM (Ramirez-Carreto et al., 2012). Pantinin-1, recently characterized from the scorpion *P. imperator* by the cDNA cloning strategy, was active against Gram-positive bacteria with a MIC of 8–32 μM. Pantinin-1 showed no hemolysis at MIC and only mild hemolysis at the higher concentration of 64 μM (21%, human erythrocytes) (Zeng et al., 2013). These three examples demonstrate that natural scorpion AMPs can be found with good therapeutic indexes. They are by themselves good candidates for antimicrobial drug development.

The remaining AMPs found in scorpion venoms for which the hemolysis activities were assayed, were reported as highly hemotoxic. This does not mean that they are not valuable in the search for alternative antibiotics. Several studies have shown that the potential of AMPs for clinical applications can be optimized by improving their antimicrobial activity and reducing their toxicity against human cells (Fjell et al., 2012; Huang et al., 2010). This has also been demonstrated with scorpion AMPs. Analogs of natural scorpion AMPs could be potential anti-infective drugs, even for treating antibiotic-resistant pathogens. Mucroporin, an antimicrobial peptide synthesized from a sequence found in a cDNA library from *Lychas mucronatus*, was moderately effective against Gram-positive bacterial strains, including clinically isolated pathogens. An engineered peptide, Mucroporin-M1, was designed from the sequence of Mucroporin by replacing the amino acid residues at the hydrophilic side of the predicted α-helix with positively charged residues. Mucroporin-M1 showed improved antibacterial activity against Gram-positive bacteria, Gram-negative bacteria, and clinically isolated antibiotic-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS), penicillin-resistant *S. aureus* (PRSA) and penicillin-resistant *Staphylococcus epidermidis* (PRSE) (Dai et al., 2008). The same group applied a similar approach to produce a potent variant of BmKn2, an antimicrobial peptide derived from the venom of the scorpion *M. martensii* Karsch (Zeng et al., 2004). The Kn2-7 variant showed increased inhibitory activity against both Gram-negative and Gram-positive bacteria, being even more effective against clinical antibiotic-resistant strains of MRSA, MRCNS, PRSA and PRSE, than the original BmKn2. The hemolytic activity of Kn2-7 was also significantly improved. The HC_{50} value of the wild-type peptide BmKn2 (90 μg/ml) was drastically decreased for the mutant peptide Kn2-7 (17 μg/ml). It is even more relevant that, in an *S. aureus* mouse skin infection model, the topical application of Kn2-7 effectively protected the skin of mice from infection (Cao et al., 2012). These two examples demonstrate that the native scorpion AMPs can also be effectively used as scaffolds for the design of more potent and specific antibiotics.

Contrary to classical antibiotics, the ligand-independent mechanism of bactericidal action of most AMPs implies that they are likely to be effective against clinical strains of antibiotic-resistant and multi-resistant pathogens. Within the scorpion AMPs this capacity was demonstrated for Mucroporin-M1, BmKn2 and its Kn2-7 variant, as mentioned above, and the following ones. Imcroporin, derived from a cDNA library of the scorpion *Isometrus maculates*, was the first peptide of scorpion venom origin to show potent antimicrobial activity against antibiotic resistant gram-positive pathogen strains such as MRSA, MRCNS and PRSE. The MIC of imcroporin against the PRSE (50 μg/ml) was 20-fold lower than that of penicillin G. Against MRSA and MRCNS strains (also 50 μg/ml) it was two- and eight-fold lower than the MIC of cefotaxime, respectively. Significantly, the *in vivo* activity of imcroporin was also demonstrated in a mouse model infected with *S. aureus*. A 60 mg/kg dose of imcroporin was able to cope with 10 LD_{50} of intraperitoneally injected bacteria, with a 100% survival ratio, a result equivalent to the use of the same dose of vancomycin (Zhao et al., 2009). Ctriporin is a potent antimicrobial peptide identified from a cDNA library of *Chaerilus tricostatus*. Ctriporin was effective against MRSA with a MIC of 10 μg/ml, 400 to 2000 times better than penicillin G and 10 to 40 times better than cefotaxime. Against PRSE, with a MIC of 10 μg/ml, it was 1000 times more effective than penicillin G. Ctriporin was effective when used as a topical antibiotic treatment in an *S. aureus* mouse skin wound infection model (Fan et al., 2011). Vejovine is an antimicrobial peptide purified from the venom of the scorpion *V. mexicanus smithi*. Vejovine inhibited growth of clinical isolates of Gram-negative multidrug resistant strains of *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumanii*, with MICs of 4.4–50 μM. This peptide also displayed hemolytic activity against human erythrocytes with a HC_{50} of 100 μM (Hernandez-Aponte et al., 2011). Recently, using a rational approach, several variants were designed using vejovine and its homolog hadrurin as templates, with the aim of improving their antimicrobial and hemolytic properties. Indeed, the variants resulted more potent than the parental peptides against the same Gram-negative multidrug resistant strains (with MICs of 0.8–25 μM), and also less hemolytic (HC_{50} up to 900 μM), which represents a dramatic improvement in their therapeutic indexes (Sanchez-Vasquez et al., 2013). This work constitutes an encouraging example of the results that can be achieved by the rational design of novel prospective antimicrobial peptides with potential clinical applications using the natural scorpion AMPs as scaffolds.

It was recently demonstrated that AMPs could be combined with classical antibiotics to obtain an additive or even a synergistic effect on the inhibition of bacterial growth (Garcia et al., 2013). This finding opens a new window of opportunities for the clinical application of mixed formulations of commercial antibiotics and AMPs. The possibility of employing low concentrations of fast killing AMPs (to circumvent their cytotoxicity against mammalian

cells) together with commercial antibiotics is very attractive and should be thoroughly explored in the future.

2.2. Antifungal peptides

Infections by opportunistic fungal pathogens have become a major clinical problem in the past decades, with increased morbidity and mortality. Many immunocompromised patients are highly susceptible to fungal infections: transplant recipients under immunosuppressive therapy, cancer patients treated with cytotoxic drugs, and AIDS patients. The most important fungal pathogens are the yeasts of the genus *Candida*, *Cryptococcus neoformans*, and the mold *Aspergillus fumigatus*. Infections caused by these fungi range from superficial mucosal infections, like oral candidiasis, to life-threatening systemic infections, such as disseminated candidiasis, cryptococcal meningitis or invasive aspergillosis (Sternberg, 1994). Fungi can become resistant to antifungal drugs by specific mechanisms or by more generic ones, e.g., by actively transporting them out of the cell through multidrug efflux pumps (Morschhauser, 2010). It is thus relevant to find new candidates for antifungal drugs that can cope with the resistance mechanisms.

Several scorpion NDBPs have been tested for antifungal activity. Some of them are active against pathogens of clinical importance. Opistoporin 1 and parabutoporin inhibited 50% growth (IC_{50}) of the yeast *Saccharomyces cerevisiae* (Murphy and Kavanagh, 1999) at a concentration of 2 μM (Moerman et al., 2002). Pandinin2 can inhibit the growth of *Candida albicans* (Pfaller and Diekema, 2007) with a MIC of 19.1 μM (Corzo et al., 2001). Meucin 18 was active against *A. fumigatus* (Rinaldi, 1983), *C. albicans* and *S. cerevisiae*, with lethal concentrations (C_L) of 8.3 μM, 25.1 μM, and 10.9 μM, respectively (Gao et al., 2009). Ctriporin was effective against *C. albicans* at a MIC of 20 μg/ml (Fan et al., 2011). Pantinin-1, -2 and -3, inhibited the growth of *Candida tropicalis* (Chai et al., 2010) with MIC of 16 μM, 16 μM and 17 μM, respectively (Zeng et al., 2013). A modified peptide from *Androctonus amoreuxi*, AamAP-S1, was effective against *C. albicans* at a MIC of 5 μM, over 10 times more potent than its parental peptide AmAP1, another example of the possibilities of peptide engineering for improving AMP qualities (Almaaytah et al., 2012).

2.3. Antimalarial peptides

More than 3 billion people are at risk of malaria, which is endemic in more than a hundred countries. Children in sub-Saharan Africa and Southeast Asia have the highest risk of contracting and dying from malaria (Murray et al., 2012). Global morbidity and mortality from malaria has decreased substantially in the last years, but still roughly 2000 people die every day from *Plasmodium falciparum* infection. Two factors are largely responsible for these decrements: increased deployment of insecticide-treated bednets and increased availability of highly effective artemisinin combination treatments. The effort to eradicate malaria faces many challenges, including the development of pyrethroid resistance in some *Anopheles* mosquitoes, and the emergence of artemisinin resistance in *P. falciparum* in Southeast Asia (White et al., 2014). One of the driving forces in the appearance of resistance is the exposure of the parasite population to artemisinin monotherapies for many years. This phenomenon has resurfaced the need for alternative therapeutics against malaria.

The first described antimalarial scorpion peptide was scorpine. It is a peptide with three disulfide bridges, isolated from the venom of the scorpion *P. imperator* (Conde et al., 2000). Scorpine showed a potent inhibitory effect on two key stages of *Plasmodium berghei* development. Although *P. berghei* does not affect humans, it functions as a rodent model for malaria, since it goes through the same stages of development as *P. falciparum* after the infection with gametocytes by a mosquito bite. Scorpine was able to inhibit the development of *P. berghei* at the ookinete (with a median effective dose, ED_{50}, of 0.7 μM) and gamete (with an ED_{50} of 10 μM) stages of the parasite's development. It is also worth noting that scorpine was one of the first antimalarial peptides that found their way into the most recent and promising technology for antimalarial weapons. Transgenic entomopathogenic fungus *Metarhizium anisopliae*, engineered to express scorpine, was able to block transmission of *Plasmodium* by mosquitoes with advanced infections (Fang et al., 2011).

Two reports of scorpion-derived NDBPs with antimalarial activity are available. In the first one, clones from a cDNA library from the scorpion *Mesobuthus eupeus* venom gland were identified, which encode for NDBPs meucin-24 and meucin-25. Though not related to each other in terms of structure or sequence, both synthetic peptides were able to inhibit the development of *P. berghei* ookinetes in the concentration range from 10 to 20 μM. Moreover, they were able to actually kill intraerythrocytic *P. falciparum* at a concentration of 10 μM. They significantly reduced parasite density 48 h post-treatment, and completely eliminated the parasite from the erythrocytes after 72 h. Remarkably, meucin-24 and meucin-25 were selective against *Plasmodium* with no detected toxicity to bacteria and fungi at the concentrations used. Also, no hemolytic effect on mouse erythrocytes was registered even at 100 μM concentration (Gao et al., 2010). Meucin-24 and meucin-25 are undoubtedly strong candidates for antimalarial therapies. The other report involved the above-mentioned AMPs derived from vejovine and hadrurin, which displayed antibacterial activity. When their antimalarial activity was tested, the results showed that some of the designed variants inhibited the formation of ookinetes from *P. berghei* by 40% at 5 μM, doubling this percentage when the concentration was increased to 25 μM (Sanchez-Vasquez et al., 2013).

2.4. Antiviral peptides

Newly emerging viral infections represent a major threat to human health. Traditionally, vaccine development has been an extremely effective strategy to protect from specific viral infections. The problem is that a functional vaccine cannot be produced until sufficient quantities of the emerging virus are available for vaccine manufacture. And the manufacturing process itself takes precious time. This implies that the population cannot be protected with a specific product for a length of time. In addition, newly emerging viruses frequently exhibit gene rearrangements, and each individual viral strain must be first identified and characterized, since unfortunately, very often, the vaccines against a particular infectious strain do not protect against a rearranged one (Burke and Fish, 2009). This situation highlights the relevance of the development of more generic antiviral therapeutics.

A few scorpion peptides display themselves as effective antiviral peptides (AVP). The first reported one was Hp1090, discovered in a cDNA library from the venomous gland of the scorpion *Heterometrus petersii*. Hp1090 inhibited hepatitis C virus (HCV) infection *in vitro*, with an IC_{50} of 5 μM. At roughly 13 μM, Hp1090 inhibited the amplification of HCV RNA in Huh7.5.1 cells with a higher potency than IFN-α. Hp1090 prevents the initiation of HCV infection by directly interacting with viral particles and rapidly disrupting their phospholipid membranes (Yan et al., 2011). This AVP is a very good candidate for the development of a therapeutic agent for hepatitis C. The optimized mucroporin-M1 was mentioned before in regard to its antimicrobial activity. Besides that, mucroporin-M1 also demonstrated antiviral activities against measles virus (EC_{50} of 3.52 μM), against the SARS coronavirus (EC_{50} of 7.12 μM), and against Influenza A virus subtype H5N1 (EC_{50} of 1.03 μM).

Paradoxically, the original peptide mucroporin showed no antiviral activity against any of these three viruses (Li et al., 2011). The discovery of the antiviral activities of mucroporin-M1 indicates that cationic peptides from scorpion venom could represent good candidates for the development of multifunctional antiviral agents. The already mentioned scorpion venom peptide derivative Kn2-7 was identified as a potent anti-HIV-1 peptide with an EC_{50} value of 1.65 μM while showing low cytotoxicity to host cells. Kn2-7 was able to inhibit all 13 members of a standard reference panel of HIV-1 subtype B pseudotyped viruses (PV) regardless of their tropism. Roughly 9 μM of Kn2-7 almost completely inhibited viral replication of both cell-free and cell-associated replication-competent HIV-1. The anti-HIV-1 activity was correlated with a direct interaction between Kn2-7 and the HIV-1 envelope, once again demonstrating that an AVP can rapidly and directly disrupt viral membranes. In this same study, BmKn2, the parental peptide of Kn2-7, and mucroporin-M1 were also shown to display anti-HIV-1 activity, though to a lesser extent (Chen et al., 2012). Ctry2459, a peptide derived from a cDNA library from the scorpion *Chaerilus tryznai* has been proven to inhibit HCV infection by directly inactivating infectious viral particles. However, Ctry2459 was not able to suppress an established infection due to its low bioavailability to infected cells. Based on the Ctry2459 sequence, two new histidine-rich peptides were designed, Ctry2459-H2 and Ctry2459-H3, with the aim of enhancing cellular uptake and improving intracellular distribution. The mutated peptides significantly suppressed the established HCV infection at the cellular level, while showing even lower cytotoxic and hemolytic activities than the parental peptide. This effective design strategy for enhancing the bioavailability of peptide drugs could also be applied to other AMPs and AVPs (Hong et al., 2013). Recently, two venom peptides from the scorpion *H. petersii* were identified with effective inhibitory effect on herpes simplex virus type 1 (HSV-1) infection *in vitro*. The Hp1036 and Hp1239 peptides exhibited potent viruscidal activities against HSV-1 (EC_{50} of 0.43 μM and 0.41 μM, respectively) as the result of the destruction of the viral morphology. They also showed effective inhibitory effects when added at the different stages of the HSV-1 life cycle: attachment, entry and post entry, which means that the peptides were able to enter the host cells and reduce the intracellular viral infectivity. Hp1036 and Hp1239 are also good candidates for the development of antiviral drugs.

2.5. Bradykinin-potentiating peptides

Bradykinin is a physiologically and pharmacologically active peptide of the kinin group of proteins. It increases blood vessels vasodilation and capillary permeability, and therefore causes arterial blood pressure to fall. It is a substrate for the angiotensin-converting enzyme (ACE), a proteolytic enzyme that inactivates bradykinin. ACE inhibitors are therefore valuable tools for the treatment of hypertension. The discovery of the bradykinin-potentiating peptides (BPPs) led to the development of captopril, an ACE inhibitor derived from a peptide found in the venom of the lancehead viper *Bothrops jararaca*. Nowadays, millions of hypertensive patients worldwide are treated with ACE inhibitors (Camargo et al., 2012).

The first scorpion peptide shown to display bradykinin-potentiating activities was Peptide T, isolated from the venom of the scorpion *Tityus serrulatus*. Peptide T potentiated the contractile activity of bradykinin on the isolated guinea pig ileum, and inhibited the hydrolysis of bradykinin by the angiotensin-converting enzyme. It also increased the depressor effect of bradykinin on arterial blood pressure in a rat model (Ferreira et al., 1993). Peptide K_{12}, isolated from the venom of the scorpion *Buthus occitanus* was able to potentiate the bradykinin effect on the isolated guinea pig ileum as well as on the isolated rat uterus. The peptide also strongly potentiated the depressor effect of bradykinin on arterial blood pressure in rats. Peptide K_{12} inhibited ACE, and was not proteolysed by the enzyme (Meki et al., 1995). It is very interesting that the C-terminal region of BmKbpp, the AMP peptide mentioned before, shows significant sequence similarity with the peptide K_{12}. Indeed, BmKbpp and its C-terminal fragment (BmKbpp-C) displayed bradykinin-potentiating activity. Although less potent than peptide K12, at a concentration of 50 nM, both BmKbpp and BmKbpp-C induced significant shifts of the dose–response curve of muscular contraction induced by bradykinin, with BmKbpp-C being more active than the whole peptide. This suggests that both BmKbpp and BmKbpp-C have bradykinin potentiating activity, and the activity of BmKbpp-C is stronger than that of BmKbpp (Zeng et al., 2012).

It is worth mentioning here that some scorpion peptides can potentiate bradykinin through mechanisms different than ACE inhibition, which seems to be the case for *T. serrulatus* hypotensins (TsHpt). TsHpt-I and a synthetic peptide comprising its C-terminus (TsHpt-$I_{[17–25]}$) were able to potentiate the hypotensive effects of bradykinin in normotensive rats. A relevant hypotensive effect, independent of bradykinin, was also observed for both TsHpt-I and TsHpt-$I_{[17–25]}$. These two peptides were able to induce an endothelium-dependent vasorelaxation of aortic rings from rats, a process also dependent on nitric oxide release. Hypotensins do not inhibit ACE, so other mechanisms (probably the improvement of the endothelial function) might be relevant in blood pressure control, which deserve to be more deeply studied (Verano-Braga et al., 2008).

2.6. Autoimmunity-targeting potassium channels blockers

The voltage-gated K^+ channel (Kv) was proposed as a target for immunosupression because 4-aminopyridine, a K^+ channel blocker, inhibits T cell proliferation and interleukine-2 secretion (DeCoursey et al., 1984). These findings were subsequently confirmed by Koo et al. They found that margatoxin, a Kv1.3-selective peptide; isolated from the *Centruroides margaritatus* scorpion venom suppresses delayed-type hypersensitivity in guinea pigs, providing evidence that Kv1.3 blockade can inhibit immune response *in vivo* (Koo et al., 1997). During the last decade several compounds that block Kv1.3 channels were shown to prevent the delayed-type hypersensitivity reaction and improve the symptoms of various experimental animal models of autoimmune diseases (Beeton et al., 2001a, 2001b, 2006; Valverde et al., 2004).

Many toxin peptides targeting the Kv1.3 channel have been identified as good drug candidates, with Kd ranging from picomolar to micromolar values (Chandy et al., 2004; Panyi et al., 2006). Vm24, a 36 amino acids peptide isolated from the venom of the scorpion *V. mexicanus smithi* (Gurrola et al., 2012) inhibits Kv1.3 channels of human lymphocytes with a Kd of 2.9 pM and exhibits at least 1500-fold selectivity for Kv1.3 over other ion channels assayed. The application of picomolar concentrations of Vm24 inhibits the proliferation and Ca^{2+} signaling of human T cells *in vitro* and reduces delayed-type hypersensitivity reactions in rats *in vivo*, without significant side effects involving general immunosuppression. The characteristics mentioned above confer Vm24 a therapeutic potential for several T-cell mediated autoimmune diseases including multiple sclerosis, type-1 diabetes, rheumatoid arthritis, and psoriasis, among other immunological diseases (Varga et al., 2012).

Scorpion toxins have served as structural templates used to bioengineer novel molecular therapeutics for the treatment of T-cell mediated autoimmune disease. The bioengineered OSK-1 [E16K, K20D] is a synthetic toxin based on the template sequence of the OSK-1 peptide, isolated from the *Orthochirus scrobiculosus*

scorpion venom. This toxin displays an increased affinity, approximately five times greater for Kv1.3 than that of the native peptide (Mouhat et al., 2005). Another potent and highly selective inhibitor of Kv1.3 is the peptide ADWX-1 (IC_{50} of 1.89 pM) which was designed using the structure of BmKTX as template. BmKTX is a peptide isolated from the venom of the scorpion *M. martensii* Karsch (Renisio et al., 2000). Three non-native mutations were engineered into ADWX-1 (G11R, I28T, and D33H) which increase its affinity 100-fold over the native BmKTX (*K*d of 0.2 nM) (Han et al., 2008). Another example of a synthetic toxin that was designed using scorpion toxins as structural templates is mokatoxin-1. It was designed and identified using a phage display library of 11,200 *de novo* proteins, using the α-KTx scaffold of 31 scorpion toxin sequences known or predicted to bind to potassium channels. Mokatoxin-1 is highly specific for Kv1.3 (Takacs et al., 2009).

The bioengineering of scorpion peptides represents a valuable area of research and a potential tool of bioactive scaffolds for the development of novel drugs used in the treatment of several pathologies in which potassium channels are involved.

2.7. Immuno-modulators

The *T. serrulatus* venom (TsV) is able to activate the complement system, as evidenced by the decreased serum lytic activity, activation of C3 and factor B and the induction of leukocyte chemotaxis (Bertazzi et al., 2005).

In cases of severe scorpion envenomation, a systemic inflammatory response is triggered, with the release of inflammatory cytokines that contribute to immunological imbalance, multiple organ dysfunction and death (Magalhaes et al., 1999; Petricevich, 2010). High levels of pro-inflammatory and anti-inflammatory cytokines in human serum have been reported after scorpion envenomation (revised in Petricevich, 2010). Scorpion venom also induces an increase in the neutrophil count in blood and a simultaneous reduction in the mature neutrophil count in the bone marrow of the rat. This blood neutrophilia is a consequence of the mobilization of neutrophils from the bone marrow which in turn is dependent on the activation of platelet-activating factor receptors (Borges et al., 2000).

Studies performed with the *T. serrulatus* venom and/or its major toxins, showed an inmunomodulatory activity in macrophages. High levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8 and IL-10 were observed in supernatants of macrophages from mice exposed to *T. serrulatus* venom and its major toxins (Fialho et al., 2011; Petricevich et al., 2007). In the same way, increased levels of IL-1α, IL-1β, IL-6 and IL-10 were observed in sera from mice exposed to *Centruroides noxius* scorpion venom (Petricevich, 2006). Depending on the concentrations used, TsV, Toxin 1 (Ts1) and Toxin 6 (Ts6) stimulated the production of nitric oxide (NO), IL-6 and TNF-α in J774.1 cells. Toxin 2 (Ts2) alone stimulated the production of IL-10, suggesting an anti-inflammatory activity of Ts2. These findings are important for the basic understanding of the mechanisms involved in macrophage activation following scorpion envenomation (Zoccal et al., 2011). Using knockout mice it has been demonstrated that TsV interacts with Toll-like receptors (TLR) 2, TLR4 and CD14, a cell surface receptor that cooperates with TLR4. This interaction recruits myeloid differentiation factor (MyD88) and activates the activator protein 1(AP-1) and NF-kB pathways. Similarly, Ts1 induces TNF-α and IL-6 production in a manner that is dependent on TLR2, TLR4 and CD14, although signaling occurs mainly through NF-kB activation (Zoccal et al., 2014).

The data mentioned above indicate that scorpion venoms have an important immuno-modulatory effect on macrophages and give us important information for the understanding of scorpion envenomation and the mechanisms involved in macrophage activation following envenomation. This information widens the research field of scorpion venom as a useful biotechnological tool to treat immune-mediated diseases.

It has been reported that some NDBPs found in scorpion venoms such as parabutoporin and opistoporin, in addition to having antibacterial and antifungal activity, also presented immunomodulating activity. These peptides at micromolar concentrations are able to interact with the cell membrane and form pores, thus exercising their antimicrobial, antifungal and hemolytic activity. However at lower concentrations these same peptides can activate the chemotaxis and exocytosis or inhibit the production of superoxide in granulocytes (Willems et al., 2002).

Parabutoporin was isolated from the venom of the scorpion *P. schlechteri* and opistoptoporin from the venom of the scorpion *O. carinatus*. These are amphipatic α-helical peptides of 45 and 44 amino acids respectively. Both peptides are capable of inducing a reversible release of Ca^{2+} from the intracellular stores of Ca^{2+} of granulocyte-like HL60 cells. The release of calcium was sensitive to Pertussis toxin, indicating that the release of Ca^{2+} involves G proteins (Moerman et al., 2003). It has been shown that parabutoporin inhibits the activation of the NADPH oxidase by acting as a competitive inhibitor of Protein Kinase B (Akt), thus contributing to the decline of superoxide production by human neutrophils (Remijsen et al., 2006). Parabutoporin delayed neutrophil apoptosis via lipid raft-dependent activation of Akt (Remijsen et al., 2009). It has been shown that parabutoporin also stimulates neutrophil motility through the activation of Pertussis toxin sensitive signaling pathways through the up-regulation of GTP bound Rac2 levels and possibly through the interaction of G proteins as proposed earlier (Remijsen et al., 2010). The previously mentioned BmKbpp, besides its antimicrobial and antifungal activities at micromolar concentrations, also inhibits the superoxide production in granulocytes or Hl-60 cells at sub-micromolar concentrations (Zeng et al., 2012). Parabutoporin, opistoporin and BmKbpp are long chain multifunctional peptides that have been classified (on the principles of pharmacological activity, sequence similarity and peptide length) together with hadrurin (Torres-Larios et al., 2000), pandinin1 (Corzo et al., 2001), Im-1 (Miyashita et al., 2010) vejovine (Hernandez-Aponte et al., 2011) and mauriporin (Almaaytah et al., 2013), so these last peptides might have the same functional properties as parabutoporin, opistoporin and BmKbpp (Almaaytah and Albalas, 2014). These multifunctional peptides with antimicrobial and immune-regulatory activity provide an interesting tool for pharmaceutical design.

2.8. Anticancer peptides

According to estimates from the International Agency for Research on Cancer (IARC), there were 14.1 million new cancer cases and 8.2 million cancer deaths worldwide in 2012. These numbers for 2008 were 12.7 and 7.6 millions, respectively. So cancer is on the rise globally, mainly because of the aging and growth of the world population (Ferlay et al., 2013). The last decades have seen significant progress in both the diagnosis and the therapeutic approaches for cancer treatment. Despite favorable advancements, the classical methods available today, surgery, radiation and chemotherapy, still show a relatively low success rate and a high risk of reoccurrence. The lack of adequate selectivity for tumor cells and, therefore, the unspecific targeting of healthy cells with many deleterious side effects seriously limit the effectiveness of available chemotherapeutics (Morgan et al., 2004). The search for more specific and selective anticancer drugs, either designed *de novo* or derived from natural compounds, will remain a very active field in the foreseeable future.

Anticancer peptides represent an important resource for the design of tumor-targeting drugs that could allow tackling the cancer development process from different angles. Some of these small molecules display efficient tissue penetration and uptake by the heterogeneous cancer cells. They could act on tumors directly by their intrinsic activity, by synergizing with existing chemotherapeutics, or by functioning as carrier vehicles for drugs with lower selectivity or bioavailability (Gaspar et al., 2013). Scorpion venom components are a promising source of biologically active molecules with a potential to fight cancer. Some scorpion proteins and peptides have shown both *in vitro* and *in vivo* effects on cancer cells, with one of them even reaching phase I and phase II clinical trials (Heinen and da Veiga, 2011).

Chlorotoxin (ClTx, UniprotKB P45639) is a peptide containing 36 amino acids and 4 disulfide bonds, purified from the venom of the scorpion *Leiurus quinquestriatus* (DeBin et al., 1993). It possesses a single tyrosine residue available for radioiodination. Its solution structure, determined by NMR spectroscopy, consists of a small three-stranded antiparallel β-sheet cross-linked to an α-helix through three disulfide bonds and the fourth one links the small N-terminal beta strand to the rest of the molecule, characterizing the peptide as a knottin (Lippens et al., 1995). The earliest study showed ClTx is able to block small-conductance Cl^- channels, derived from epithelial cells (DeBin et al., 1993). Then, its binding to chloride channels specifically expressed on human astrocytoma and glioma cells was also shown (Ullrich et al., 1998, 1995; Ullrich and Sontheimer, 1996). These experiments allowed the identification of the voltage-activated chloride channels present in astrocytes. Indeed, it has been shown that ClTx inhibits these chloride channels by its binding to metalloprotease-2 (MMP-2) (Deshane et al., 2003; Mamelak and Jacoby, 2007). ClTx causes the endocytosis of MMP-2 with ClC-3, a subtype of Cl^- channel upregulated in glioma membranes, depleting the cell-surface of Cl-channels. ClTx effectively blocked the migration of STTGI and U251-MG human glioma cells, but ion channel depletion alone was not able to fully block glioma cell invasion (Lui et al., 2010). The ClTx-MMP-2 complex interaction has been shown to be specific to neuroectodermal cells of glioma and tumors. ClTx does not bind to normal human tissues, including neuronal cells (DeBin et al., 1993; Lyons et al., 2002). More recently it was shown that ClTx-modified liposomes are capable of significantly inhibit breast tumor 4T1 growth, an aggressive metastatic breast cancer cell line derived from a BALB/c mouse mammary tumor, which highly expresses MMP-2, as well as increasing the antimetastasis effect (Qin et al., 2014). A different vehicle, a nanocapsule exhibiting the monomeric fusion of chlorotoxin to the amino terminus of the human IgG-Fc (M-ClTx-Fc), was internalized and inhibited the migration of pancreatic cancer cells (El-Ghlban et al., 2014). Many groups have been working in the elaboration of nanoparticles conjugated with chlorotoxin specific to glioma, either to access/treat this cancer or to monitor/visualize the tumor growth (a recent revision is presented in Fu et al. (2012)). ClTx has also been used *in vivo* and *in vitro* to improve the anticancer activity of chemotherapy drugs, such as doxorubicin, an anthracycline antibiotic used to reduce or inhibit cancer cells growth (Xiang et al., 2011). ClTx was used as a ligand to direct more effectively stable nucleic acid lipid particles (SNALPs) transporting small interfering RNAs (siRNAs) and antisense oligonucleotides (asOs) to glioblastoma both *in vitro* and *in vivo* (Costa et al., 2013). Transmolecular Industries developed a synthetic ClTx and its commercial equivalent (TM601) was approved by the FDA for clinical testing. Besides having antitumoral activity, TM601 presents anti-angiogenic properties. TM601 was able to inhibit angiogenesis both *in vitro* and *in vivo* stimulated by many factors and potentiate the anti-angiogenic effect of bevacizumab, a monoclonal antibody that attaches to the vascular endothelial growth factor (VEGF), inhibiting the establishment of new blood vessels to feed the tumor. Further, TM601 effectively inhibited neovascularization induced by basic fibroblast growth factor (bFGF) and tumor necrosis factor (TNFα) whereas bevacizumab did not (Jacoby et al., 2010). In addition to the inhibition of glioma cells growth and invasion and angiogenesis *in vivo*, ClTx is able to cross the blood–brain barrier (BBB) (Hockaday et al., 2005). These unique properties made ClTx an ideal candidate for clinical trials in glioma.

In a phase I study, iodinated ^{131}I-TM-601 was intracavitarly administrated to 18 patients with recurrent malignant glioma. The radiolabeled TM-601 presented increased life-time in tumor area, when compared to normal brain, specificity to surgical cavity, no grade 3 or 4 toxicities, and it was well tolerated. Besides, some of these patients didn't show any progression of the tumor for 30 months (Mamelak et al., 2006). Consequently, a phase II study was initiated in the United States enrolling patients from 17 centers presenting recurrent glioma. The results showed survival improvement and were made known during the annual meeting of the Neuro-Oncology Society in 2009 (Shen et al., 2009), and widely noticed by medical newspapers. Phase I/II clinical trials with ^{131}I-TM-601 also showed it is an important imaging tool for determining the extent of neoplastic growth (Hockaday et al., 2005). A bioconjugate consisting of ClTx and the fluorescent compound Cy5.5 has been successfully used to demarcate cancer cells from the surrounding normal cells in patients, increasing the chance to remove cancer cells without damaging healthy cells (Stroud et al., 2011).

Chlorotoxin is a very specific agent for diagnosis and treatment of glioma, being BBB permeable, nontoxic and nonimmunogenic. It has been considered as a successful targeting drug to glioblastoma, giving hopes for this cancer's cure (Mrugala et al., 2012).

A cDNA sequence encoding for a four disulfide bridged short chain toxin, named Bm-12 or BmKCT, was cloned from the venom gland of *M. martensii* Karsch. It showed 68% identity to chlorotoxin isolated from *L. quinquestriatus* (Wu et al., 2000; Yang et al., 2005). The recombinant BmKCT (rBmKCT) reversibly inhibited chloride currents of single glioma cells (U2251) (Yang et al., 2005), as well as of human glioma (SHG-44) cells, which also had the proliferation inhibited by the toxin while normal astrocytes were not affected (Fu et al., 2007). rBmKCT was intraperitonealy administered to normal mice and histological analysis showed damage in brain, leg muscle and cardiac muscle (Fu et al., 2007). ^{131}I-BmKCT specifically conjugated with C6 glioma cells and inhibited the cell growth *in vitro* (Zhao et al., 2010). The recombinant GST-BmKCT inhibited the growth and the metastasis of C6 glioma cells *in vivo* in rats, and the ^{131}I-labeled or Cy5.5-conjugated rGST-BmKCT targeted specifically to glioma *in situ* (Fan et al., 2010). The combination therapy of BmKCT and LiCl synergistically inhibited migration, invasion and proliferation of C6 glioma cells, accompanied by diminished activity of metalloproteinase-2 (Fu et al., 2007). More recently, a delivery system based on a recombinant replication-defective adenovirus (Ad) was constructed to serve as the vehicle to transport the BmKCT gene to the C6 glioma cells (Du et al., 2013). These authors showed that Ad-BmKCT significantly inhibited the tumor proliferation in mice in a time-dependent manner.

From the cDNA library made from the venom gland of *M. martensii* Karsch, the sequence of BmK AGAP was identified, possessing high identity to the sodium channel modulator α-toxins (Zeng et al., 2000). Later, it was shown that BmK AGAP presents analgesic and antitumoral activities (Liu et al., 2003; Lui et al., 2010; Zhao et al., 2011). BmK AGAP analgesic activity was verified on hot-plate and mouse twisting assays (Liu et al., 2003). The antitumor activity was shown *in vivo* in S-180 fibrosarcoma and Ehrlich ascites tumor models, where BmK AGAP increased the survival period and

decreased the tumor size at 1 mg/kg mouse body weight (Liu et al., 2003). The recombinant rBmK AGAP (rAGAP) inhibited the proliferation of glioma cells leading to cell cycle arrest in G1 phase and suppression of proteins related to cell cycle regulation and cell growth (Zhao et al., 2011). Recently, a new peptide holding 94% identity to BmK AGAP was isolated from the venom of the same scorpion species, and also presented the dual-function with analgesic and antitumor activities. It was named BmK AGAP-SYPU2 (Shao et al., 2014).

A 39-amino-acid peptide named margatoxin (MgTx) was isolated from the venom of *C. margaritatus*, and inhibited n-type current of human T-lymphocytes ($K_v1.3$ channel), with no significant effect on $K_v1.5$, $K_v3.1$, ISK (a slowly activating K^+ channel cloned from smooth muscle and heart), Maxi-K channels and on the delayed rectifier of mouse pancreatic β cells (Garcia-Calvo et al., 1993). MgTx inhibited the cell proliferation of human lung adenocarcinoma A549 cell line, leading to a significant increment of the G1 phase and a decrease of the S phase, a mechanism involving $p21^{Waf1/Cip1}$ accumulation, and decrease of Cdk4 and cyclin D3 (Jang et al., 2011). The same authors showed an *in vivo* tumor volume reduction in mice after injection of MgTx.

Iberiotoxin (IbTx), a 37-amino acid peptide presenting 68% sequence identity to charybdotoxin (ChTX), was purified from the venom of *Mesobuthus tumulus*, and showed to be a selective blocker of high conductance calcium-activated (maxi-K, also known as BK-channel) potassium channels (Galvez et al., 1990). In human 1321N1 astrocytoma cells, the inhibition of BK-channels by IbTx abolished the K^+-channel induced proliferation (Basrai et al., 2002). The inhibition of BK-channels by IbTx arrested glioma cells in the S phase and induced cell death (Weaver et al., 2004). IbTx inhibited the growth of the hormone insensitive prostate cancer cell line PC-3, where there is an amplification and functional overexpression of the KCNMA1 gene that encodes to the pore-forming α-subunit of the Maxi-K channel (Bloch et al., 2007).

Charybdotoxin (ChTx), purified from the venom of *L. quinquestriatus hebraeus*, has 37 amino acid residues, and inhibits calcium-activated potassium channels (Gimenez-Gallego et al., 1988). ChTx is not selective for Ca^{2+}-activated K^+ channel (Schweitz et al., 1989). ChTx inhibited the migration of NIH3T3 fibroblasts and human melanoma cells, possibly reducing the electrochemical driving force for Ca^{2+} entry, by K^+ channel blockage (Schwab et al., 1999).

The whole venom of *Heterometrus bengalensis* presents antiproliferative and apoptogenic activity on human leukemic cell lines U937 and K562 (Das Gupta et al., 2007). Later, a high molecular weight protein (72 kDa) was identified, named bengalin, which has the anticancer activity against the human leukemic cell lines through induction of apoptosis, predominantly mediated by the mitochondrial pathway with the participation of pro and anti-apoptotic proteins, and with no significant death of normal human lymphocytes (Das Gupta et al., 2010). A more recent work showed cell death induced by bengalin can occur by an alternate pathway other than apoptosis that could be autophagic in nature (Das Gupta et al., 2013). Bengalin also presents anti-osteoporosis activity by its capacity of restoring bone minerals, and cardiotoxicity and neurotoxicity as demonstrated in *in vivo* experiments (Haldar et al., 2010).

TsAP-1 and -2 are two non disulphide-bridged amidated peptides isolated from the venom of the Brazilian yellow scorpion, *T. serrulatus*, which present antimicrobial and anticancer activities (Guo et al., 2013). They are very similar to each other; however, the higher helical content and hydrophobic moment of TsAP-2 as compared to TsAP-1 explain the divergence in antimicrobial activities. Synthetic analogs with increased cationicity, reduced the antimicrobial activity but enhanced the anticancer cell activity evaluated on H157 (oral squamous carcinoma), H838 (lung adenocarcinoma), MCF-7 (breast carcinoma), PC3 (prostate carcinoma) and U251-MG (glioblastoma) cancer cells (Guo et al., 2013).

Neopladines 1 and 2 were purified from the venom of *Tityus discrepans*, and consist of proteins of 29,918 Da and 30,388 Da molecular masses, respectively. They presented apoptotic activity on SKBR3 human breast carcinoma cells through the activation of Fas signaling by induction of FasL expression (D'suze et al., 2010).

BmHYA1 is a hyaluronidase enzyme purified from *M. martensi* Karsh with molecular mass of 48,696 Da, and the capacity to digest a wide range of hyaluronan fragments (Feng et al., 2008). It is known that hyaluronan is up-regulated in breast cancer, and is related to the aggressiveness of different tumors (Anttila et al., 2000). BmHYA1 removed hyaluronan from the MDAMB-231 breast cancer cell line, which led to the down-regulation of a variant of CD44, a protein highly expressed in cancer cells (Feng et al., 2008).

Maurocalcine (MCa) is a 33 amino acid residues peptide isolated from *Scorpio maurus palmatus* that acts on the ryanodine receptor (RyR) (Fajloun et al., 2000). As Imperatoxin A (IpTxa), from *P. imperator*, the first scorpion toxin with capacity to bind to RyR with high affinity and specificity (Valdivia et al., 1992), they share structural identity to a segment of the II–III loop of the skeletal muscle dihydropyridine receptor hat has been proposed to act as an activator of the RyR1 (Fajloun et al., 2000). There are 4 known scorpion calcins with the capacity to act on RyR, and together with many other peptides able to translocate across the plasma membrane within seconds to minutes, are termed cell-penetrating peptides (CPPs) (Howl et al., 2007). For instance, maurocalcine was efficiently used as an intracellular delivery agent for doxorubicin (Dox) in low- and high-invasive breast carcinoma MCF7 and MDA-MB 231 cells (which are Dox-resistant and Dox-sensitive cell lines, respectively) *in vitro*. On the Dox-resistant cell line, the coupling of Dox to maurocalcine allowed to overcome the drug resistance (Aroui et al., 2009). Many MCa analogs with low toxicity or shorter length were designed and their ability to drive different compounds to the intracellular space was proved (Conde et al., 2000; Tisseyre et al., 2013; reviewed in Poillot and De Waard (2011)). Among the possible applications, are the diagnostic tools based on coupling MCa to dyes and nanoparticles (Jayagopal et al., 2009), and the theragnostic applications, by means of coupling MCa to radioactive material (Tisseyre et al., 2014).

Be it directly-acting antitumor therapeutics, diagnostic tags, adjuvants or just carriers for other relevant moieties, scorpion-derived molecules have shown their potential as tools for the fight on cancer.

3. Concluding remarks

It is clear that the large diversity of scorpion venom components represents a treasure in natural compounds that could eventually find their way into pharmaceuticals. The potential applications of newly described molecules will probably continue to fuel the scorpion venom research in the foreseeable future. With only a tiny fraction of the whole universe of venom components expected to exist in the more than 1700 different species being characterized thus far, the possibilities seem endless.

Ethical statement

The authors declare that this manuscript complies with the Elsevier Ethical Guidelines for Journal Publication.

Acknowledgments

This work was partially supported by a collaboration program granted by the Mexican Council of Science and Technology (CONACyT, grants 153496 and 122094) of Mexico and the Brazilian National Council of Research (CNPq) given to ESF and LDP. Additional support came from *Dirección General de Asuntos del Personal Académico* (DGAPA) of UNAM (grant IN200113 to LDP, and CNPq (306524/2012-0) to EFS.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.toxicon.2014.11.233.

References

Alekshun, M.N., Levy, S.B., 2007. Molecular mechanisms of antibacterial multidrug resistance. Cell 128, 1037–1050.
Almaaytah, A., Albalas, Q., 2014. Scorpion venom peptides with no disulfide bridges: a review. Peptides 51, 35–45.
Almaaytah, A., Tarazi, S., Mhaidat, N.M., Al-Balas, Q., Mukattash, T.L., 2013. Mauriporin, a novel cationic α-helical peptide with selective cytotoxic activity against prostate cancer cell lines from the venom of the scorpion Androctonus mauritanicus. Int. J. Pept. Res. Ther. 19, 281–293.
Almaaytah, A., Zhou, M., Wang, L., Chen, T., Walker, B., Shaw, C., 2012. Antimicrobial/cytolytic peptides from the venom of the North African scorpion, Androctonus amoreuxi: biochemical and functional characterization of natural peptides and a single site-substituted analog. Peptides 35, 291–299.
Anttila, M.A., Tammi, R.H., Tammi, M.I., Syrjanen, K.J., Saarikoski, S.V., Kosma, V.M., 2000. High levels of stromal hyaluronan predict poor disease outcome in epithelial ovarian cancer. Cancer Res. 60, 150–155.
Aroui, S., Ram, N., Appaix, F., Ronjat, M., Kenani, A., Pirollet, F., De Waard, M., 2009. Maurocalcine as a non toxic drug carrier overcomes doxorubicin resistance in the cancer cell line MDA-MB 231. Pharm. Res.-Dord. 26, 836–845.
Basrai, D., Kraft, R., Bollensdorff, C., Liebmann, L., Benndorf, K., Patt, S., 2002. BK channel blockers inhibit potassium-induced proliferation of human astrocytoma cells. Neuroreport 13, 403–407.
Beeton, C., Barbaria, J., Giraud, P., Devaux, J., Benoliel, A.M., Gola, M., Sabatier, J.M., Bernard, D., Crest, M., Beraud, E., 2001a. Selective blocking of voltage-gated K^+ channels improves experimental autoimmune encephalomyelitis and inhibits T cell activation. J. Immunol. 166, 936–944.
Beeton, C., Wulff, H., Barbaria, J., Clot-Faybesse, O., Pennington, M., Bernard, D., Cahalan, M.D., Chandy, K.G., Beraud, E., 2001b. Selective blockade of T lymphocyte K(+) channels ameliorates experimental autoimmune encephalomyelitis, a model for multiple sclerosis. Proc. Natl. Acad. Sci. U. S. A. 98, 13942–13947.
Beeton, C., Wulff, H., Standifer, N.E., Azam, P., Mullen, K.M., Pennington, M.W., Kolski-Andreaco, A., Wei, E., Grino, A., Counts, D.R., Wang, P.H., LeeHealey, C.J., Andrews, B.S., Sankaranarayanan, A., Homerick, D., Roeck, W.W., Tehranzadeh, J., Stanhope, K.L., Zimin, P., Havel, P.J., Griffey, S., Knaus, H.G., Nepom, G.T., Gutman, G.A., Calabresi, P.A., Chandy, K.G., 2006. Kv1.3 channels are a therapeutic target for T cell-mediated autoimmune diseases. Proc. Natl. Acad. Sci. U. S. A. 103, 17414–17419.
Bertazzi, D.T., de Assis-Pandochi, A.I., Talhaferro, V.L., Caleiro Seixas Azzolini, A.E., Pereira Crott, L.S., Arantes, E.C., 2005. Activation of the complement system and leukocyte recruitment by Tityus serrulatus scorpion venom. Int. Immunopharmacol. 5, 1077–1084.
Bloch, M., Ousingsawat, J., Simon, R., Schraml, P., Gasser, T.C., Mihatsch, M.J., Kunzelmann, K., Bubendorf, L., 2007. KCNMA1 gene amplification promotes tumor cell proliferation in human prostate cancer. Oncogene 26, 2525–2534.
Borges, C.M., Silveira, M.R., Aparecida, M., Beker, C.L., Freire-Maia, L., Teixeira, M.M., 2000. Scorpion venom-induced neutrophilia is inhibited by a PAF receptor antagonist in the rat. J. Leukoc. Biol. 67, 515–519.
Bosmans, F., Tytgat, J., 2007. Voltage-gated sodium channel modulation by scorpion alpha-toxins. Toxicon 49, 142–158.
Burke, J.D., Fish, E.N., 2009. Antiviral strategies: the present and beyond. Curr. Mol. Pharmacol. 2, 32–39.
Camargo, A.C., Ianzer, D., Guerreiro, J.R., Serrano, S.M., 2012. Bradykinin-potentiating peptides: beyond captopril. Toxicon 59, 516–523.
Cao, L., Dai, C., Li, Z., Fan, Z., Song, Y., Wu, Y., Cao, Z., Li, W., 2012. Antibacterial activity and mechanism of a scorpion venom peptide derivative in vitro and in vivo. PLoS One 7, e40135.
Chai, L.Y., Denning, D.W., Warn, P., 2010. Candida tropicalis in human disease. Crit. Rev. Microbiol. 36, 282–298.
Chandy, K.G., Wulff, H., Beeton, C., Pennington, M., Gutman, G.A., Cahalan, M.D., 2004. K^+ channels as targets for specific immunomodulation. Trends Pharmacol. Sci. 25, 280–289.
Chen, Y., Cao, L., Zhong, M., Zhang, Y., Han, C., Li, Q., Yang, J., Zhou, D., Shi, W., He, B., Liu, F., Yu, J., Sun, Y., Cao, Y., Li, Y., Li, W., Guo, D., Cao, Z., Yan, H., 2012. Anti-HIV-1 activity of a new scorpion venom peptide derivative Kn2-7. PLoS One 7, e34947.
Chippaux, J.P., 2012. Emerging options for the management of scorpion stings. Drug Des. Dev. Ther. 6, 165–173.
Chippaux, J.P., Goyffon, M., 2008. Epidemiology of scorpionism: a global appraisal. Acta Trop. 107, 71–79.
Conde, R., Zamudio, F.Z., Rodriguez, M.H., Possani, L.D., 2000. Scorpine, an anti-malaria and anti-bacterial agent purified from scorpion venom. FEBS Lett. 471, 165–168.
Corzo, G., Escoubas, P., Villegas, E., Barnham, K.J., He, W., Norton, R.S., Nakajima, T., 2001. Characterization of unique amphipathic antimicrobial peptides from venom of the scorpion Pandinus imperator. Biochem. J. 359, 35–45.
Costa, P.M., Cardoso, A.L., Mendonca, L.S., Serani, A., Custodia, C., Conceicao, M., Simoes, S., Moreira, J.N., Pereira de Almeida, L., Pedroso de Lima, M.C., 2013. Tumor-targeted chlorotoxin-coupled nanoparticles for nucleic acid delivery to glioblastoma cells: a promising system for glioblastoma treatment. Mol. Ther. Nucleic Acids 2, e100.
D'suze, G., Rosales, A., Salazar, V., Sevcik, C., 2010. Apoptogenic peptides from Tityus discrepans scorpion venom acting against the SKBR3 breast cancer cell line. Toxicon 56, 1497–1505.
Dai, C., Ma, Y., Zhao, Z., Zhao, R., Wang, Q., Wu, Y., Cao, Z., Li, W., 2008. Mucroporin, the first cationic host defense peptide from the venom of Lychas mucronatus. Antimicrob. Agents Chemother. 52, 3967–3972.
Dai, L., Yasuda, A., Naoki, H., Corzo, G., Andriantsiferana, M., Nakajima, T., 2001. IsCT, a novel cytotoxic linear peptide from scorpion Opisthacanthus madagascariensis. Biochem. Biophys. Res. Commun. 286, 820–825.
Das Gupta, S., Debnath, A., Saha, A., Giri, B., Tripathi, G., Vedasiromoni, J.R., Gomes, A., Gomes, A., 2007. Indian black scorpion (Heterometrus bengalensis Koch) venom induced antiproliferative and apoptogenic activity against human leukemic cell lines U937 and K562. Leuk. Res. 31, 817–825.
Das Gupta, S., Gomes, A., Debnath, A., Saha, A., Gomes, A., 2010. Apoptosis induction in human leukemic cells by a novel protein Bengalin, isolated from Indian black scorpion venom: through mitochondrial pathway and inhibition of heat shock proteins. Chem.-Biol. Interact. 183, 293–303.
Das Gupta, S., Halder, B., Gomes, A., Gomes, A., 2013. Bengalin initiates autophagic cell death through ERK-MAPK pathway following suppression of apoptosis in human leukemic U937 cells. Life Sci. 93, 271–276.
DeBin, J.A., Maggio, J.E., Strichartz, G.R., 1993. Purification and characterization of chlorotoxin, a chloride channel ligand from the venom of the scorpion. Am. J. Physiol. 264, C361–C369.
DeCoursey, T.E., Chandy, K.G., Gupta, S., Cahalan, M.D., 1984. Voltage-gated K^+ channels in human T lymphocytes: a role in mitogenesis? Nature 307, 465–468.
Deshane, J., Garner, C.C., Sontheimer, H., 2003. Chlorotoxin inhibits glioma cell invasion via matrix metalloproteinase-2. J. Biol. Chem. 278, 4135–4144.
Diaz-Garcia, A., Morier-Diaz, L., Frion-Herrera, Y., Rodriguez-Sanchez, H., Caballero-Lorenzo, Y., Mendoza-Llanes, D., Riquenes-Garlobo, Y., Fraga-Castro, J.A., 2013. In vitro anticancer effect of venom from Cuban scorpion Rhopalurus junceus against a panel of human cancer cell lines. J. Venom Res. 4, 5–12.
Du, J., Fu, Y.J., Wang, J.N., Liang, A.H., 2013. Adenovirus-mediated expression of BmK CT suppresses growth and invasion of rat C6 glioma cells. Biotechnol. Lett. 35, 861–870.
El-Ghlban, S., Kasai, T., Shigehiro, T., Yin, H.X., Sekhar, S., Ida, M., Sanchez, A., Mizutani, A., Kudoh, T., Murakami, H., Seno, M., 2014. Chlorotoxin-Fc fusion inhibits release of MMP-2 from pancreatic cancer cells. Biomed. Res. Int. 2014, 152659.
Fajloun, Z., Kharrat, R., Chen, L., Lecomte, C., Di Luccio, E., Bichet, D., El Ayeb, M., Rochat, H., Allen, P.D., Pessah, I.N., De Waard, M., Sabatier, J.M., 2000. Chemical synthesis and characterization of maurocalcine, a scorpion toxin that activates Ca^{2+} release channel/ryanodine receptors. FEBS Lett. 469, 179–185.
Fan, S.Z., Sun, Z.B., Jiang, D.H., Dai, C., Ma, Y.B., Zhao, Z.H., Liu, H., Wu, Y.L., Cao, Z.J., Li, W.X., 2010. BmKCT toxin inhibits glioma proliferation and tumor metastasis. Cancer Lett. 291, 158–166.
Fan, Z., Cao, L., He, Y., Hu, J., Di, Z., Wu, Y., Li, W., Cao, Z., 2011. Ctriporin, a new anti-methicillin-resistant Staphylococcus aureus peptide from the venom of the scorpion Chaerilus tricostatus. Antimicrob. Agents Chemother. 55, 5220–5229.
Fang, W., Vega-Rodriguez, J., Ghosh, A.K., Jacobs-Lorena, M., Kang, A., St Leger, R.J., 2011. Development of transgenic fungi that kill human malaria parasites in mosquitoes. Science 331, 1074–1077.
Feng, L., Gao, R., Gopalakrishnakone, P., 2008. Isolation and characterization of a hyaluronidase from the venom of Chinese red scorpion Buthus martensi. Comp. Biochem. Phys. C 148, 250–257.
Ferlay, J., Soerjomataram, I., Ervik, M., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D., Bray, F., 2013. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. International Agency for Research on Cancer.
Ferreira, L.A., Alves, E.W., Henriques, O.B., 1993. Peptide T, a novel bradykinin potentiator isolated from Tityus serrulatus scorpion venom. Toxicon 31, 941–947.
Fialho, E.M., Maciel, M.C., Silva, A.C., Reis, A.S., Assuncao, A.K., Fortes, T.S., Silva, L.A., Guerra, R.N., Kwasniewski, F.H., Nascimento, F.R., 2011. Immune cells recruitment and activation by Tityus serrulatus scorpion venom. Toxicon 58, 480–485.
Fjell, C.D., Hiss, J.A., Hancock, R.E., Schneider, G., 2012. Designing antimicrobial peptides: form follows function. Nat. Rev. Drug Discov. 11, 37–51.
Fu, Y.J., An, N., Li, K., Zheng, Y.L., Liang, A.H., 2012. Chlorotoxin-conjugated nanoparticles as potential glioma-targeted drugs. J. Neuro.-Oncol. 107, 457–462.

Fu, Y.J., Yin, L.T., Liang, A.H., Zhang, C.F., Wang, W., Chai, B.F., Yang, J.Y., Fan, X.J., 2007. Therapeutic potential of chlorotoxin-like neurotoxin from the Chinese scorpion for human gliomas. Neurosci. Lett. 412, 62–67.

Galvez, A., Gimenez-Gallego, G., Reuben, J.P., Roy-Contancin, L., Feigenbaum, P., Kaczorowski, G.J., Garcia, M.L., 1990. Purification and characterization of a unique, potent, peptidyl probe for the high conductance calcium-activated potassium channel from venom of the scorpion Buthus tamulus. J. Biol. Chem. 265, 11083–11090.

Gao, B., Sherman, P., Luo, L., Bowie, J., Zhu, S., 2009. Structural and functional characterization of two genetically related meucin peptides highlights evolutionary divergence and convergence in antimicrobial peptides. FASEB J. 23, 1230–1245.

Gao, B., Xu, J., Rodriguez Mdel, C., Lanz-Mendoza, H., Hernandez-Rivas, R., Du, W., Zhu, S., 2010. Characterization of two linear cationic antimalarial peptides in the scorpion Mesobuthus eupeus. Biochimie 92, 350–359.

Garcia, F., Villegas, E., Espino-Solis, G.P., Rodriguez, A., Paniagua-Solis, J.F., Sandoval-Lopez, G., Possani, L.D., Corzo, G., 2013. Antimicrobial peptides from arachnid venoms and their microbicidal activity in the presence of commercial antibiotics. J. Antibiot. 66, 3–10.

Garcia-Calvo, M., Leonard, R.J., Novick, J., Stevens, S.P., Schmalhofer, W., Kaczorowski, G.J., Garcia, M.L., 1993. Purification, characterization, and biosynthesis of margatoxin, a component of Centruroides margaritatus venom that selectively inhibits voltage-dependent potassium channels. J. Biol. Chem. 268, 18866–18874.

Gaspar, D., Veiga, A.S., Castanho, M.A., 2013. From antimicrobial to anticancer peptides. A review. Front. Microbiol. 4, 294.

Gimenez-Gallego, G., Navia, M.A., Reuben, J.P., Katz, G.M., Kaczorowski, G.J., Garcia, M.L., 1988. Purification, sequence, and model structure of charybdotoxin, a potent selective inhibitor of calcium-activated potassium channels. Proc. Natl. Acad. Sci. U. S. A. 85, 3329–3333.

Goudet, C., Chi, C.W., Tytgat, J., 2002. An overview of toxins and genes from the venom of the Asian scorpion Buthus martensi Karsch. Toxicon 40, 1239–1258.

Gould, I.M., Bal, A.M., 2013. New antibiotic agents in the pipeline and how they can help overcome microbial resistance. Virulence 4, 185–191.

Guo, X.X., Ma, C.B., Du, Q., Wei, R., Wang, L., Zhou, M., Chen, T.B., Shaw, C., 2013. Two peptides, TsAP-1 and TsAP-2, from the venom of the Brazilian yellow scorpion, Tityus serrulatus: evaluation of their antimicrobial and anticancer activities. Biochimie 95, 1784–1794.

Gurrola, G.B., Hernandez-Lopez, R.A., Rodriguez de la Vega, R.C., Varga, Z., Batista, C.V., Salas-Castillo, S.P., Panyi, G., del Rio-Portilla, F., Possani, L.D., 2012. Structure, function, and chemical synthesis of Vaejovis mexicanus peptide 24: a novel potent blocker of Kv1.3 potassium channels of human T lymphocytes. Biochemistry 51, 4049–4061.

Haldar, S., Das Gupta, S., Gomes, A., Giri, B., Dasgupta, S.C., Biswas, A., Mishra, R., Gomes, A., 2010. A high molecular weight protein Bengalin from the Indian black scorpion (Heterometrus bengalensis CL Koch) venom having anti-osteoporosis activity in female albino rats. Toxicon 55, 455–461.

Han, S., Yi, H., Yin, S.J., Chen, Z.Y., Liu, H., Cao, Z.J., Wu, Y.L., Li, W.X., 2008. Structural basis of a potent peptide inhibitor designed for Kv1.3 channel, a therapeutic target of autoimmune disease. J. Biol. Chem. 283, 19058–19065.

Hancock, R.E., Sahl, H.G., 2006. Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. Nat. Biotechnol. 24, 1551–1557.

Harrison, P.L., Abdel-Rahman, M.A., Miller, K., Strong, P.N., 2014. Antimicrobial peptides from scorpion venoms. Toxicon 88C, 115–137.

Heinen, T.E., da Veiga, A.B., 2011. Arthropod venoms and cancer. Toxicon 57, 497–511.

Hernandez-Aponte, C.A., Silva-Sanchez, J., Quintero-Hernandez, V., Rodriguez-Romero, A., Balderas, C., Possani, L.D., Gurrola, G.B., 2011. Vejovine, a new antibiotic from the scorpion venom of Vaejovis mexicanus. Toxicon 57, 84–92.

Hockaday, D.C., Shen, S., Fiveash, J., Raubitschek, A., Colcher, D., Liu, A., Alvarez, V., Mamelak, A.N., 2005. Imaging glioma extent with 131I-TM-601. J. Nucl. Med. 46, 580–586.

Hong, W., Zhang, R., Di, Z., He, Y., Zhao, Z., Hu, J., Wu, Y., Li, W., Cao, Z., 2013. Design of histidine-rich peptides with enhanced bioavailability and inhibitory activity against hepatitis C virus. Biomaterials 34, 3511–3522.

Howl, J., Nicholl, I.D., Jones, S., 2007. The many futures for cell-penetrating peptides: how soon is now? Biochem. Soc. Trans. 35, 767–769.

Huang, Y., Huang, J., Chen, Y., 2010. Alpha-helical cationic antimicrobial peptides: relationships of structure and function. Protein Cell 1, 143–152.

Isbister, G.K., Bawaskar, H.S., 2014. Scorpion envenomation. N. Engl. J. Med. 371, 457–463.

Jacoby, D.B., Dyskin, E., Yalcin, M., Kesavan, K., Dahlberg, W., Ratliff, J., Johnson, E.W., Mousa, S.A., 2010. Potent pleiotropic anti-angiogenic effects of TM601, a synthetic chlorotoxin peptide. Anticancer Res. 30, 39–46.

Jang, S.H., Choi, S.Y., Ryu, P.D., Lee, S.Y., 2011. Anti-proliferative effect of Kv1.3 blockers in A549 human lung adenocarcinoma in vitro and in vivo. Eur. J. Pharmacol. 651, 26–32.

Jayagopal, A., Su, Y.R., Blakemore, J.L., Linton, M.F., Fazio, S., Haselton, F.R., 2009. Quantum dot mediated imaging of atherosclerosis. Nanotechnology 20.

Koo, G.C., Blake, J.T., Talento, A., Nguyen, M., Lin, S., Sirotina, A., Shah, K., Mulvany, K., Hora Jr., D., Cunningham, P., Wunderler, D.L., McManus, O.B., Slaughter, R., Bugianesi, R., Felix, J., Garcia, M., Williamson, J., Kaczorowski, G., Sigal, N.H., Springer, M.S., Feeney, W., 1997. Blockade of the voltage-gated potassium channel Kv1.3 inhibits immune responses in vivo. J. Immunol. 158, 5120–5128.

Kuhn-Nentwig, L., 2003. Antimicrobial and cytolytic peptides of venomous arthropods. Cell. Mol. Life Sci. 60, 2651–2668.

Li, Q., Zhao, Z., Zhou, D., Chen, Y., Hong, W., Cao, L., Yang, J., Zhang, Y., Shi, W., Cao, Z., Wu, Y., Yan, H., Li, W., 2011. Virucidal activity of a scorpion venom peptide variant mucroporin-M1 against measles, SARS-CoV and influenza H5N1 viruses. Peptides 32, 1518–1525.

Lippens, G., Najib, J., Wodak, S.J., Tartar, A., 1995. NMR sequential assignments and solution structure of chlorotoxin, a small scorpion toxin that blocks chloride channels. Biochemistry 34, 13–21.

Liu, Y.F., Ma, R.L., Wang, S.L., Duan, Z.Y., Zhang, J.H., Wu, L.J., Wu, C.F., 2003. Expression of an antitumor-analgesic peptide from the venom of Chinese scorpion Buthus martensii Karsch in Escherichia coli. Protein Expr. Purif. 27, 253–258.

Lui, V.C.H., Lung, S.S.S., Pu, J.K.S., Hung, K.N., Leung, G.K.K., 2010. Invasion of human glioma cells is regulated by multiple chloride channels including ClC-3. Anticancer Res. 30, 4515–4524.

Lyons, S.A., O'Neal, J., Sontheimer, H., 2002. Chlorotoxin, a scorpion-derived peptide, specifically binds to gliomas and tumors of neuroectodermal origin. Glia 39, 162–173.

Magalhaes, M.M., Pereira, M.E., Amaral, C.F., Rezende, N.A., Campolina, D., Bucaretchi, F., Gazzinelli, R.T., Cunha-Melo, J.R., 1999. Serum levels of cytokines in patients envenomed by Tityus serrulatus scorpion sting. Toxicon 37, 1155–1164.

Mamelak, A.N., Jacoby, D.B., 2007. Targeted delivery of antitumoral therapy to glioma and other malignancies with synthetic chlorotoxin (TM-601). Expert Opin. Drug Del. 4, 175–186.

Mamelak, A.N., Rosenfeld, S., Bucholz, R., Raubitschek, A., Nabors, L.B., Fiveash, J.B., Shen, S., Khazaeli, M.B., Colcher, D., Liu, A., Osman, M., Guthrie, B., Schade-Bijur, S., Hablitz, D.M., Alvarez, V.L., Gonda, M.A., 2006. Phase I single-dose study of intracavitary-administered iodine-131-TM-601 in adults with recurrent high-grade glioma. J. Clin. Oncol. 24, 3644–3650.

Maroti, G., Kereszt, A., Kondorosi, E., Mergaert, P., 2011. Natural roles of antimicrobial peptides in microbes, plants and animals. Res. Microbiol. 162, 363–374.

Meki, A.R., Nassar, A.Y., Rochat, H., 1995. A bradykinin-potentiating peptide (peptide K12) isolated from the venom of Egyptian scorpion Buthus occitanus. Peptides 16, 1359–1365.

Miyashita, M., Sakai, A., Matsushita, N., Hanai, Y., Nakagawa, Y., Miyagawa, H., 2010. A novel amphipathic linear peptide with both insect toxicity and antimicrobial activity from the venom of the scorpion Isometrus maculatus. Biosci. Biotechnol. Biochem. 74, 364–369.

Moerman, L., Bosteels, S., Noppe, W., Willems, J., Clynen, E., Schoofs, L., Thevissen, K., Tytgat, J., Van Eldere, J., Van Der Walt, J., Verdonck, F., 2002. Antibacterial and antifungal properties of alpha-helical, cationic peptides in the venom of scorpions from southern Africa. Eur. J. Biochem./FEBS 269, 4799–4810.

Moerman, L., Verdonck, F., Willems, J., Tytgat, J., Bosteels, S., 2003. Antimicrobial peptides from scorpion venom induce Ca(2+) signaling in HL-60 cells. Biochem. Biophys. Res. Commun. 311, 90–97.

Mookherjee, N., Hancock, R.E., 2007. Cationic host defence peptides: innate immune regulatory peptides as a novel approach for treating infections. Cell. Mol. Life Sci. 64, 922–933.

Morgan, G., Ward, R., Barton, M., 2004. The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies. Clin. Oncol. 16, 549–560.

Morschhauser, J., 2010. Regulation of multidrug resistance in pathogenic fungi. Fungal Genet. Biol. 47, 94–106.

Mouhat, S., Visan, V., Ananthakrishnan, S., Wulff, H., Andreotti, N., Grissmer, S., Darbon, H., De Waard, M., Sabatier, J.M., 2005. K^+ channel types targeted by synthetic OSK1, a toxin from Orthochirus scrobiculosus scorpion venom. Biochem. J. 385, 95–104.

Mrugala, M.M., Adair, J.E., Kiem, H.P., 2012. Outside the box-novel therapeutic strategies for glioblastoma. Cancer J. 18, 51–58.

Murphy, A., Kavanagh, K., 1999. Emergence of Saccharomyces cerevisiae as a human pathogen: implications for biotechnology. Enzyme Microb. Technol. 25, 551–557.

Murray, C.J., Rosenfeld, L.C., Lim, S.S., Andrews, K.G., Foreman, K.J., Haring, D., Fullman, N., Naghavi, M., Lozano, R., Lopez, A.D., 2012. Global malaria mortality between 1980 and 2010: a systematic analysis. Lancet 379, 413–431.

Panyi, G., Possani, L.D., Rodriguez de la Vega, R.C., Gaspar, R., Varga, Z., 2006. K^+ channel blockers: novel tools to inhibit T cell activation leading to specific immunosuppression. Curr. Pharm. Des. 12, 2199–2220.

Petricevich, V.L., 2006. Balance between pro- and anti-inflammatory cytokines in mice treated with Centruroides noxius scorpion venom. Mediat. Inflamm. 2006, 54273.

Petricevich, V.L., 2010. Scorpion venom and the inflammatory response. Mediat. Inflamm. 2010, 903295.

Petricevich, V.L., Hernandez Cruz, A., Coronas, F.I., Possani, L.D., 2007. Toxin gamma from Tityus serrulatus scorpion venom plays an essential role in immunomodulation of macrophages. Toxicon 50, 666–675.

Pfaller, M.A., Diekema, D.J., 2007. Epidemiology of invasive candidiasis: a persistent public health problem. Clin. Microbiol. Rev. 20, 133–163.

Poillot, C., De Waard, M., 2011. Potential of cell penetrating peptides for cell drug delivery. Med. Sci. 27, 527–534.

Polis, G.A., 1990. The Biology of Scorpions. Stanford University Press, Palo Alto, California.

Qin, C., He, B., Dai, W., Zhang, H., Wang, X., Wang, J., Zhang, X., Wang, G., Yin, L., Zhang, Q., 2014. Inhibition of metastatic tumor growth and metastasis via targeting metastatic breast Cancer by chlorotoxin-modified liposomes. Mol. Pharm. 11, 3233–3241.
Quintero-Hernandez, V., Jimenez-Vargas, J.M., Gurrola, G.B., Valdivia, H.H., Possani, L.D., 2013. Scorpion venom components that affect ion-channels function. Toxicon 76, 328–342.
Quintero-Hernandez, V., Ortiz, E., Rendon-Anaya, M., Schwartz, E.F., Becerril, B., Corzo, G., Possani, L.D., 2011. Scorpion and spider venom peptides: gene cloning and peptide expression. Toxicon 58, 644–663.
Ramirez-Carreto, S., Quintero-Hernandez, V., Jimenez-Vargas, J.M., Corzo, G., Possani, L.D., Becerril, B., Ortiz, E., 2012. Gene cloning and functional characterization of four novel antimicrobial-like peptides from scorpions of the family Vaejovidae. Peptides 34, 290–295.
Remijsen, Q., Vanden Berghe, T., Parthoens, E., Asselbergh, B., Vandenabeele, P., Willems, J., 2009. Inhibition of spontaneous neutrophil apoptosis by parabutoporin acts independently of NADPH oxidase inhibition but by lipid raft-dependent stimulation of Akt. J. Leukoc. Biol. 85, 497–507.
Remijsen, Q., Verdonck, F., Willems, J., 2010. Parabutoporin, a cationic amphipathic peptide from scorpion venom: much more than an antibiotic. Toxicon 55, 180–185.
Remijsen, Q.F., Fontayne, A., Verdonck, F., Clynen, E., Schoofs, L., Willems, J., 2006. The antimicrobial peptide parabutoporin competes with p47(phox) as a PKC-substrate and inhibits NADPH oxidase in human neutrophils. FEBS Lett. 580, 6206–6210.
Renisio, J.G., Romi-Lebrun, R., Blanc, E., Bornet, O., Nakajima, T., Darbon, H., 2000. Solution structure of BmKTX, a K^+ blocker toxin from the Chinese scorpion Buthus Martensi. Proteins 38, 70–78.
Rinaldi, M.G., 1983. Invasive aspergillosis. Rev. Infect. Dis. 5, 1061–1077.
Rodriguez de la Vega, R.C., Possani, L.D., 2005. Overview of scorpion toxins specific for Na^+ channels and related peptides: biodiversity, structure-function relationships and evolution. Toxicon 46, 831–844.
Rodriguez de la Vega, R.C., Schwartz, E.F., Possani, L.D., 2010. Mining on scorpion venom biodiversity. Toxicon 56, 1155–1161.
Sanchez-Vasquez, L., Silva-Sanchez, J., Jimenez-Vargas, J.M., Rodriguez-Romero, A., Munoz-Garay, C., Rodriguez, M.C., Gurrola, G.B., Possani, L.D., 2013. Enhanced antimicrobial activity of novel synthetic peptides derived from vejovine and hadrurin. Biochim. Biophys. Acta 1830, 3427–3436.
Schwab, A., Reinhardt, J., Schneider, S.W., Gassner, B., Schuricht, B., 1999. K(+) channel-dependent migration of fibroblasts and human melanoma cells. Cell. Physiol. Biochem. 9, 126–132.
Schweitz, H., Bidard, J.N., Maes, P., Lazdunski, M., 1989. Charybdotoxin is a new member of the K^+ channel toxin family that includes Dendrotoxin-I and mast-cell degranulating peptide. Biochemistry 28, 9708–9714.
Shao, J., Zhang, R., Ge, X., Yang, B., Zhang, J., 2007. Analgesic peptides in Buthus martensii Karsch: a traditional Chinese animal medicine. Asian J. Tradit. Med. 2, 6.
Shao, J.H., Cui, Y., Zhao, M.Y., Wu, C.F., Liu, Y.F., Zhang, J.H., 2014. Purification, characterization, and bioactivity of a new analgesic-antitumor peptide from Chinese scorpion Buthus martensii Karsch. Peptides 53, 89–96.
Shen, S., Nabors, L.B., Raizer, J., Fiveash, J., Spies, S., Costello, R., O'Neill, A.M., 2009. Single-versus multiple-dose radiopharmaceutical injections: dosimetry analysis of intracavitary 131I-TM601 in high-grade glioma patients. In: Joint Meeting of the Society for Neuro-oncology (SNO) and the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Section on Tumors, p. 663. Neuro Oncol., New Orleans, LA.
Sternberg, S., 1994. The emerging fungal threat. Science 266, 1632–1634.
Stockmann, R., Ythier, E., 2010. Scorpions of the World. N.A.P. Editions, Verrières-le-Buisson.
Stroud, M.R., Hansen, S.J., Olson, J.M., 2011. In vivo bio-imaging using chlorotoxin-based conjugates. Curr. Pharm. Des. 17, 4362–4371.
Takacs, Z., Toups, M., Kollewe, A., Johnson, E., Cuello, L.G., Driessens, G., Biancalana, M., Koide, A., Ponte, C.G., Perozo, E., Gajewski, T.F., Suarez-Kurtz, G., Koide, S., Goldstein, S.A., 2009. A designer ligand specific for Kv1.3 channels from a scorpion neurotoxin-based library. Proc. Natl. Acad. Sci. U. S. A. 106, 22211–22216.
Tisseyre, C., Ahmadi, M., Bacot, S., Dardevet, L., Perret, P., Ronjat, M., Fagret, D., Usson, Y., Ghezzi, C., De Waard, M., 2014. Quantitative evaluation of the cell penetrating properties of an iodinated Tyr-l-maurocalcine analog. Biochim. Biophys. Acta.
Tisseyre, C., Bahembera, E., Dardevet, L., Sabatier, J.M., Ronjat, M., De Waard, M., 2013. Cell penetration properties of a highly efficient mini maurocalcine peptide. Pharmaceuticals 6, 320–339.
Torres-Larios, A., Gurrola, G.B., Zamudio, F.Z., Possani, L.D., 2000. Hadrurin, a new antimicrobial peptide from the venom of the scorpion Hadrurus aztecus. Eur. J. Biochem./FEBS 267, 5023–5031.
Ullrich, N., Bordey, A., Gillespie, G.Y., Sontheimer, H., 1998. Expression of voltage-activated chloride currents in acute slices of human gliomas. Neuroscience 83, 1161–1173.
Ullrich, N., Gillespie, G.Y., Sontheimer, H., 1995. Human astrocytoma cells express a unique chloride current. Neuroreport 7, 343–347.
Ullrich, N., Sontheimer, H., 1996. Biophysical and pharmacological characterization of chloride currents in human astrocytoma cells. Am. J. Physiol. 270, C1511–C1521.
Valdivia, H.H., Kirby, M.S., Lederer, W.J., Coronado, R., 1992. Scorpion toxins targeted against the sarcoplasmic-reticulum Ca^{2+}-release channel of skeletal and cardiac-muscle. Proc. Natl. Acad. Sci. U. S. A. 89, 12185–12189.
Valverde, P., Kawai, T., Taubman, M.A., 2004. Selective blockade of voltage-gated potassium channels reduces inflammatory bone resorption in experimental periodontal disease. J. Bone Miner. Res. 19, 155–164.
Varga, Z., Gurrola-Briones, G., Papp, F., Rodriguez de la Vega, R.C., Pedraza-Alva, G., Tajhya, R.B., Gaspar, R., Cardenas, L., Rosenstein, Y., Beeton, C., Possani, L.D., Panyi, G., 2012. Vm24, a natural immunosuppressive peptide, potently and selectively blocks Kv1.3 potassium channels of human T cells. Mol. Pharm. 82, 372–382.
Verano-Braga, T., Rocha-Resende, C., Silva, D.M., Ianzer, D., Martin-Eauclaire, M.F., Bougis, P.E., de Lima, M.E., Santos, R.A., Pimenta, A.M., 2008. Tityus serrulatus hypotensins: a new family of peptides from scorpion venom. Biochem. Biophys. Res. Commun. 371, 515–520.
Wang, G., Li, X., Wang, Z., 2009. APD2: the updated antimicrobial peptide database and its application in peptide design. Nucleic Acids Res. 37, D933–D937.
Weaver, A.K., Liu, X., Sontheimer, H., 2004. Role for calcium-activated potassium channels (BK) in growth control of human malignant glioma cells. J. Neurosci. Res. 78, 224–234.
White, N.J., Pukrittayakamee, S., Hien, T.T., Faiz, M.A., Mokuolu, O.A., Dondorp, A.M., 2014. Malaria. Lancet 383, 723–735.
Willems, J., Noppe, W., Moerman, L., van der Walt, J., Verdonck, F., 2002. Cationic peptides from scorpion venom can stimulate and inhibit polymorphonuclear granulocytes. Toxicon 40, 1679–1683.
Wu, J.J., Dai, L., Lan, Z.D., Chi, C.W., 2000. The gene cloning and sequencing of Bm-12, a chlorotoxin-like peptide from the scorpion Buthus martensi Karsch. Toxicon 38, 661–668.
Xiang, Y., Liang, L., Wang, X.Q., Wang, J.C., Zhang, X., Zhang, Q., 2011. Chloride channel-mediated brain glioma targeting of chlorotoxin-modified doxorubicine-loaded liposomes. J. Control Release 152, 402–410.
Yan, R., Zhao, Z., He, Y., Wu, L., Cai, D., Hong, W., Wu, Y., Cao, Z., Zheng, C., Li, W., 2011. A new natural alpha-helical peptide from the venom of the scorpion Heterometrus petersii kills HCV. Peptides 32, 11–19.
Yang, R., Peng, F., Liu, H., Cao, Z.J., Li, W.X., Mao, X., Jiang, D.H., 2005. Functional analysis of a gene encoding a chlorotoxin-like peptide derived from scorpion toxin. Chin. J. Biochem. Mol. Biol. 21, 5.
Zeng, X.C., Corzo, G., Hahin, R., 2005. Scorpion venom peptides without disulfide bridges. IUBMB Life 57, 13–21.
Zeng, X.C., Li, W.X., Zhu, S.Y., Peng, F., Jiang, D.H., Yang, F.H., Wu, K.L., 2000. Cloning and characterization of the cDNA sequences of two venom peptides from Chinese scorpion Buthus martensii Karsch (BmK). Toxicon 38, 893–899.
Zeng, X.C., Wang, S., Nie, Y., Zhang, L., Luo, X., 2012. Characterization of BmKbpp, a multifunctional peptide from the Chinese scorpion Mesobuthus martensii Karsch: gaining insight into a new mechanism for the functional diversification of scorpion venom peptides. Peptides 33, 44–51.
Zeng, X.C., Wang, S.X., Li, W.X., 2002. Identification of BmKAPi, a novel type of scorpion venom peptide with peculiar disulfide bridge pattern from Buthus martensii Karsch. Toxicon 40, 1719–1722.
Zeng, X.C., Wang, S.X., Zhu, Y., Zhu, S.Y., Li, W.X., 2004. Identification and functional characterization of novel scorpion venom peptides with no disulfide bridge from Buthus martensii Karsch. Peptides 25, 143–150.
Zeng, X.C., Zhou, L., Shi, W., Luo, X., Zhang, L., Nie, Y., Wang, J., Wu, S., Cao, B., Cao, H., 2013. Three new antimicrobial peptides from the scorpion Pandinus imperator. Peptides 45, 28–34.
Zhao, J.H., Qiao, W.L., Zhang, Y.N., Shao, X.X., 2010. Preparation and in vitro evaluation of I-131-BmK CT as a glioma-targeted agent. Cancer Biother. Radiol. 25, 353–359.
Zhao, Y., Cai, X., Ye, T., Huo, J., Liu, C., Zhang, S., Cao, P., 2011. Analgesic-antitumor peptide inhibits proliferation and migration of SHG-44 human malignant glioma cells. J. Cell. Biochem. 112, 2424–2434.
Zhao, Z., Ma, Y., Dai, C., Zhao, R., Li, S., Wu, Y., Cao, Z., Li, W., 2009. Imcroporin, a new cationic antimicrobial peptide from the venom of the scorpion Isometrus maculates. Antimicrob. Agents Chemother. 53, 3472–3477.
Zoccal, K.F., Bitencourt Cda, S., Paula-Silva, F.W., Sorgi, C.A., de Castro Figueiredo Bordon, K., Arantes, E.C., Faccioli, L.H., 2014. TLR2, TLR4 and CD14 recognize venom-associated molecular patterns from Tityus serrulatus to induce macrophage-derived inflammatory mediators. PLoS One 9, e88174.
Zoccal, K.F., Bitencourt Cda, S., Secatto, A., Sorgi, C.A., Bordon Kde, C., Sampaio, S.V., Arantes, E.C., Faccioli, L.H., 2011. Tityus serrulatus venom and toxins Ts1, Ts2 and Ts6 induce macrophage activation and production of immune mediators. Toxicon 57, 1101–1108.